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Proposed Registration Decision PRD2015-27

Noviflumuron

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Overview

Proposed Registration Decision for Noviflumuron

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Noviflumuron Technical Insecticide, Noviflumuron 50% Manufacturing Concentrate and Recruit HD Termite Bait, containing the technical grade active ingredient noviflumuron, to control colonies of subterranean termites to protect structures from termite damage.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Noviflumuron Technical Insecticide, Noviflumuron 50% Manufacturing Concentrate and Recruit HD Termite Bait.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on Noviflumuron, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on Noviflumuron, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Noviflumuron?

Noviflumuron is an insect growth regulator that prevents juvenile termites from developing into adults by disrupting chitin synthesis. Chitin is the main component of the termite exoskeleton. Noviflumuron is the active ingredient in the proposed commercial class product, Recruit HD Termite Bait.

Health Considerations

Can Approved Uses of Noviflumuron Affect Human Health?

Recruit HD Termite Bait, containing noviflumuron, is unlikely to affect your health when used according to label directions.

Potential exposure to noviflumuron may occur when handling and installing or monitoring the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the technical grade active ingredient noviflumuron was of low acute toxicity via the oral, dermal and inhalation routes of exposure, was non-irritating to the skin and minimally irritating to the eye, and did not produce an allergic skin reaction. The manufacturing concentrate, Noviflumuron 50% Manufacturing Concentrate, was of low acute toxicity via the oral, dermal and inhalation routes of exposure, was non-irritating to the skin and eyes, and did not produce an allergic skin reaction. The end-use product, Recruit HD Termite Bait, is a solid bait product that contains a very low level of active ingredient. Recruit HD Termite Bait is

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.
[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

considered of low acute toxicity via the oral, dermal and inhalation routes of exposure, and is not considered a potential skin or eye irritant, or a skin allergen. These conclusions were based on the physical form of the bait as well as the low acute toxicity of the active ingredient and other ingredients in the product. No acute hazard labelling is required for the technical grade active ingredient, manufacturing concentrate, or end-use product.

Applicant-supplied short-, and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of noviflumuron to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoint used for risk assessment was reduced fertility. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Risks in Residential and Other Non-Occupational Environments

Non-occupational exposure is not of concern and is considered to be negligible provided that the Recruit HD Termite Bait is used with the Sentricon Colony Elimination System bait station according to label directions.

Occupational Risks From Handling Noviflumuron

Occupational risks are not of concern when Recruit HD Termite Bait is used according to the label directions, which include protective measures.

A risk assessment conducted for Pest Control Operators (PCOs) installing and monitoring Recruit HD Termite Bait in Sentricon Colony Elimination System bait stations indicated that the risk is not of concern when the product is used according to label directions.

PCOs can come in direct contact with noviflumuron on the skin when installing or monitoring Recruit HD Termite Bait. Therefore the label will specify that anyone installing or monitoring Recruit HD Termite Bait must wear a long-sleeved shirt, long pants, chemical resistant gloves, shoes plus socks and safety glasses.

Environmental Considerations

What Happens When Noviflumuron Is Introduced Into the Environment?

When used according to label directions, noviflumuron does not pose an unacceptable risk to the environment.

Noviflumuron is used in a commercial bait system to protect structures from termite infestations. Very little noviflumuron is expected to reach the environment when it is used as a solid bait station to control termite activity.

Value Considerations

What Is the Value of Recruit HD Termite Bait?

Recruit HD Termite Bait represents a new method of controlling termites. Unlike traditional termite control products, it is a bait that results in the elimination of the termite colony rather than individual termites.

Recruit HD Termite Bait uses a combination of bait and the insect growth regulator noviflumuron to control subterranean termite colonies by preventing juveniles from developing into adults after they ingest the product. The use of a bait to control termites represents a new method in managing this pest in Canada. The structural pest control industry has identified a need for baits in termite management programs. Recruit HD Termite Bait targets the colony and results in less insecticide being applied compared to traditional soil treatments for termites.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Recruit HD Termite Bait to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To avoid direct contact with noviflumuron on the skin during installation and monitoring of Recruit HD Termite Bait, PCOs are required to wear a long-sleeved shirt, long pants, chemical resistant gloves, shoes plus socks and safety glasses. In addition, Recruit HD Termite Bait can only be installed in Sentricon Colony Elimination System bait stations.

Environment

Due to the limited outdoor use, the risk to environment is expected to be minimal. The labels will contain the standard precautionary statements for protecting the environment

Next Steps

Before making a final registration decision on noviflumuron, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

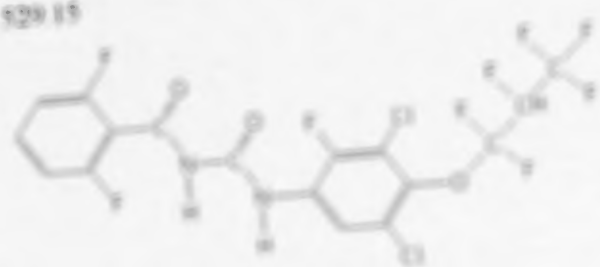
When the PMRA makes its registration decision, it will publish a Registration Decision on noviflumuron (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Novaluron

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	novaluron
Function	insect growth regulator
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	1-[3,5-dichloro-2-fluoro-4-[(*RS*)-1,1,2,3,3,3-hexafluoropropoxy]phenyl]-3-(2,6-difluorobenzoyl)urea
2. **Chemical Abstracts Service (CAS)**	*N*-[[[3,5-dichloro-2-fluoro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]amino]carbonyl]-2,6-difluorobenzamide
CAS number	121451-02-3
Molecular formula	$C_{17}H_9Cl_2F_8N_2O_4$
Molecular weight	529.15
Structural formula	
Purity of the active ingredient	99.1%

6.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Novaflumuron Technical Insecticide

Property	Result
Colour and physical state	White amorphous powder
Odour	Odourless
Melting point	168.2°C
Boiling point or range	N/A
Density	0.50 ± 0.10 g/cm³
Vapour pressure at 20°C	2.2×10^{-10} Pa
Ultraviolet (UV)-visible spectrum	Media — λ (nm) — ε (L/mol·cm) Unbuffered — 252 — 18707 Acidic — 252 — 18611 Basic — 260 — 19000
Solubility in water at 20°C	0.158 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) heptane — 0.868 n-octanol — 8.1 1,2-dichloroethane — 20.7 acetonitrile — 68.9 methanol — 88.9 p-xylene — 95.5 ethyl acetate — 200 acetone — 429
n-Octanol-water partition coefficient (K_{ow})	$\log K_{ow} = 4.30$
Dissociation constant (pK_a)	The active does not have dissociable moiety
Stability (temperature, metal)	Stable to metals and metal ions at 20°C and 50°C for 10 days

End-Use Product—Novaflumuron 50% Manufacturing Concentrate

Property	Result
Colour	Opaque white
Odour	Odourless
Physical state	Liquid
Formulation type	SC (suspension)
Guarantee	50%
Container material and description	metal and plastic jugs or drums, 1 kg to bulk

Property	Result
Density	1.380 g/mL @ 20°C
pH of 1% dispersion in water	7.93
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	Data requirement waived
Corrosion characteristics	Data requirement waived
Explodability	The product is not to be used near electrical equipment.

End Use Product – Recruit HD Termite Bait

Property	Result
Colour	Tan
Odour	Sweet
Physical state	Solid
Formulation type	RB (pellet)
Guarantee	0.5%
Container material and description	Water-soluble bag in plastic tube, 1 kg to bulk
Density	0.58 g/mL @ 23.1°C
pH of 1% dispersion in water	8.36 @ 20.3°C
Oxidizing or reducing action	The product is neither an oxidizing nor a reducing agent.
Storage stability	The product is stable for 1 year under commercial storage.
Corrosion characteristics	The product does not contain any flammable components.
Explodability	The product is not to be used near electrical equipment.

5.3 Directions for Use

Recruit HD Termite Bait is to be applied within Sentricon Colony Elimination System bait stations around structures, as well as landscape plantings and trees, to eliminate colonies of subterranean termites. Bait stations are placed underground at a maximum of 3 metre intervals around the area to be protected. Regular inspections of the bait are required, with no more than 15 months being permitted to elapse between inspections. Reapplication of the bait should be conducted when 1/3 of the bait has been consumed.

5.4 Mode of Action

Novaflumuron is an insect growth regulator belonging to mode of action group 15. It prevents termites from developing into adults by disrupting chitin synthesis. Chitin is the main component of the termite exoskeleton.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in noviflumuron technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredient in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

A high-performance liquid chromatography method with tandem mass spectrometry (HPLC-MS/MS) was developed and proposed for data generation and enforcement purposes. This method fulfills the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Method for residue analysis is summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for noviflumuron was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to noviflumuron.

In acute toxicity testing, noviflumuron was of low acute toxicity via the oral and inhalation routes in rats and via the dermal route in rabbits. In rabbits, noviflumuron was non-irritating to the skin and minimally irritating to the eyes. Noviflumuron is not a dermal sensitizer based on results from two studies in which guinea pigs were tested using the Buehler and Maximization methods.

The associated manufacturing concentrate, Noviflumuron 50% Manufacturing Concentrate, was of low acute toxicity in rats via the oral, dermal and inhalation routes. It was non-irritating to the eyes and skin of rabbits. The results of a dermal sensitization study in guinea pigs, conducted using the Buehler method, indicated that the manufacturing concentrate is not a dermal sensitizer.

Acute toxicity testing was not performed with the end-use product, Recruit HD Termite Bait. The requirement for acute toxicity studies was waived based on the very low concentration of noviflumuron in the end-use product and the low acute toxicity of the active ingredient as well as formulants contained within the product. As such, the end-use product is considered to be of low

acute toxicity via the oral, dermal and inhalation routes of exposure, and is not expected to pose an irritation or a sensitization hazard.

The absorption, distribution, metabolism and excretion of noviflumuron, uniformly radiolabelled on the fluorodichlorophenyl ring was investigated in rats following the administration of single and repeated low oral doses, a single high oral dose, and a single low intravenous dose. Noviflumuron, uniformly radiolabelled on the difluorobenzoyl ring, was also administered as a single low oral dose in these investigations. The absorption of noviflumuron from the gastrointestinal tract was moderate (approximately 35% to 56% of the administered dose) and was similar following administration of either a single low dose or multiple low doses. The results of intravenous dosing with radiolabelled noviflumuron showed that approximately 45% of the administered dose was eliminated via the feces following enterohepatic circulation. This suggested that absorption following administration of a single oral dose was likely higher than the values reported above. Following administration of a single high dose of noviflumuron, absorption from the gastrointestinal tract was reduced significantly to no more than 5% of the administered dose, suggesting saturation of absorption processes.

Elimination of orally-dosed noviflumuron occurred primarily via the feces, with fecal elimination following high-dose administration occurring more rapidly and to a greater extent than that following administration of a low dose. The majority of the radioactivity recovered in the feces consisted of unchanged noviflumuron. Urinary elimination of absorbed radioactivity was relatively slow following the administration of both low and high oral doses. Metabolites detected in urine were formed via cleavage of the acyl urea moiety followed by conjugation with glycine.

Following the administration of single or repeated low oral doses, approximately 17% to 29% of the radiolabel was retained in tissues up to seven days after dosing. The majority of this radioactivity was detected in the carcass, skin and gastrointestinal tract (with contents). Other tissues/organs showing the highest levels of radioactivity consisted of liver, kidney, fat and uterus. Only 1% of the administered dose was retained in tissues seven days after rats were given a single oral high dose of radiolabelled noviflumuron.

In a special metabolism study with the aim of determining the time-course distribution and localization of radioactivity within different regions of the brain, noviflumuron radiolabelled on the fluorodichlorophenyl ring was administered orally as a single low dose, or as ten daily low doses, to Fischer 344 rats. The results of this study demonstrated that excretion of radioactivity decreased with each successive dose and that the body burden of radioactivity increased five-fold between the first and tenth doses. The tissues with the highest levels of radioactivity seven days after the final dose were in decreasing order fat, adrenal gland, skin, ovaries, spleen and liver. Autoradiography of the brain revealed that the small amount of radioactivity that was retained in the brain was focal and localized in blood vessels on the surface in the choroid plexus of the ventricles. This finding suggested that noviflumuron does not cross the blood-brain barrier of rats after oral administration.

Short-term (28 or 90 days in duration) and long-term (one to two years in duration) toxicity studies were conducted in mice, rats and dogs via the dietary route. In a few of these studies,

only slight reductions in body weight, body weight gain, or food consumption were observed. Evidence of increased toxicity with increased duration of dosing was observed in studies conducted for 28 and 90 days, but not when comparing effects in 90-day toxicity studies to those observed after longer-term dosing. In the 90-day studies conducted in rats (Fischer 344 strain) and in dogs, partial recovery from most of the observed effects was evident after high dose animals were administered control diet for an additional 28 days.

Effects in the liver, most of which were adaptive in nature, were evident in mice, rats and dogs following repeated dietary dosing. In rats and mice, elevated liver weights and hepatocellular hypertrophy were evident after short- and long-term dosing. In the short-term mouse and rat studies, hypertrophy with altered tinctorial properties and vacuolization of the hepatocytes were observed. After two years of dosing, the incidence of basophilic foci of cellular alteration in the liver was elevated in male rats but decreased in female rats. Additional investigations conducted in high dose Fischer 344 rats after 90 days of dosing revealed increased activity of hepatic mixed function oxidases and an increase in the amount of smooth endoplasmic reticulum of centrilobular hepatocytes. Several clinical chemistry parameters related to hepatic function were also affected in rodents. These included increases in alkaline phosphatase, cholesterol, protein, and albumin, and decreases in glucose and aspartate aminotransferase. Liver effects in the dog were limited to increased liver weight after 90 days of dosing and increased cholesterol in the 90-day and one-year dietary studies.

Renal effects were manifested as increased weights in rats and dogs after short-term dietary dosing, and increased blood urea nitrogen and hyperplasia as well as mineralization of the renal pelvic epithelium in male rats after chronic dietary dosing.

The adrenal gland was affected in rats only, with increased weight observed in female Fischer 344 rats after 90 days and two years of dietary dosing, and in Sprague Dawley rats of both sexes after 90 days of dietary dosing. Pathology of the adrenal gland, in the form of hypertrophy of the zona fasciculata, was limited to Sprague Dawley rats and observed in females at lower doses than in males.

Testicular and epididymal effects were noted in selected repeat-dose dietary studies in the rat. In the 90-day dose range-finding study for the reproductive toxicity study in Sprague Dawley rats, decreases in epididymal weight as well as lower numbers and degeneration of spermatic elements in the epididymides were noted. However, no treatment-related effects on the testes or epididymides were observed in the two subsequent reproductive toxicity studies, as these tissues were not examined in the one-generation reproductive toxicity study, and the doses used in the two-generation reproductive toxicity study were lower than those that caused the effects in the 90-day dose range-finding study. Additionally, increases in testicular weight and the severity of bilateral atrophy of the seminiferous tubules, decreased epididymal weight, and bilateral aspermia were observed in noviflumuron-treated male Fischer 344 rats after two years of dosing.

Mild perturbations to hemostatic parameters were noted in a few repeat-dose dietary studies. This included increases in platelet counts in the 28-day mouse study, as well as the 90-day and one-year studies in dogs. In male Fischer 344 rats, prolonged prothrombin time was noted in the short-term and long-term studies.

Hematological effects were observed only in the dog and were manifested as changes in red blood cell parameters, increased reticulocytes and polychromasia, which were accompanied by compensatory bone marrow hyperplasia of erythroid cells. There was also an increase in total white blood cells counts, as well as a shift from lymphocytes to neutrophils in the analyses of differential white blood cell counts.

Effects on the lung and skin were observed only after chronic dietary dosing. Increased incidences of lung foci and chronic inflammation of the lung were observed in rats, while in mice, there were increased incidences of subacute to chronic lung inflammation in males and aggregates of alveolar macrophages in females. Dermal lesions were evident in rats after long-term dosing in the form of papules and pustules on the tail that were diagnosed further as hyperkeratosis and inflammation of hair follicles. In addition, necrosis of the tail was observed in male rats at higher doses.

In repeat-dose dietary studies, convulsions were observed in female mice after eight months of dosing (females were dosed higher than males in the oncogenicity study) and in Sprague Dawley rats in the 90-day reproductive toxicity dose range-finding study after ten weeks of dosing. Convulsions were not observed in studies conducted with the Fischer 344 strain of rat. In a 90-day dietary study in mice that was not submitted to the PMRA but was summarized in the report for the oncogenicity study, convulsions were reported after 11 weeks of dosing. Convulsions were also observed in the reproductive toxicity studies discussed further below.

Several neurotoxicity investigations, including functional observations and the assessment of motor activity and neuropathology, were incorporated into an interim sacrifice group dosed for one year within the two-year combined chronic toxicity/oncogenicity study in Fischer 344 rats. Treatment-related findings in this cohort of animals were limited to reduced motor activity, which occurred in females at a lower dose than in males.

There was no evidence of genotoxicity in a battery of in vivo and in vitro assays conducted with noviflumuron. Evidence of oncogenicity was apparent in both rats and mice following long-term dietary dosing. In the rat, there was an increase in the incidence of hepatocellular adenomas in males at the highest dose tested, and an increased incidence of uterine stromal polyps at the two highest doses tested. In mice, an increased incidence of hepatocellular adenomas was observed in both males and females at the highest dose tested. It should be noted that the highest dose tested in male mice was lower than the highest dose administered to female mice. In addition, the high dose that was administered to female mice was considered excessive as it resulted in an increase in mortality. All of the tumours of interest were considered benign in nature, and there was no indication of a progression to malignant neoplasms in either species. Larger and heavier commonly occurring interstitial (Leydig) cell tumors were observed in noviflumuron-treated male Fischer 344 rats after two years of dosing; however, there was no treatment-related increase in the incidence of this tumour.

In guideline gavage developmental toxicity studies in rats and rabbits, no adverse maternal or developmental effects were noted when noviflumuron was administered up to the limit dose of testing. A special, non-guideline teratology screening study was also conducted with noviflumuron, in which rat conceptuses obtained from time-mated rats on gestation day (GD) 9

were cultured for 48 hours in serum collected from rats dosed via gavage. There were no treatment-related effects on viability, growth, or morphological development of the embryos in this study.

In the assessment of the reproductive toxicity potential of noviflumuron, a one-generation dietary study initially intended as a two-generation study was terminated early due to excessive F1 pup mortality. At the high dose, nearly all pups of the F1 litters died by postnatal day (PND) 21 with the majority of deaths occurring between PND 4 and 14. High-dose F1 pups also exhibited tonoclonic convulsions and other signs of ill health. As previously noted, parental high-dose animals exhibited convulsions beginning 11 weeks after the initiation of dosing. Effects on reproductive performance were manifested at the high dose as a decrease in the number of live pups born and an increase in stillbirths. Several high-dose parental females that still had a live litter partway through the lactation phase were switched to control diet in order to evaluate the ability of the neonates to survive and possibly recover from convulsions. Of the litters for which parental females were switched to control diet during lactation, most were lost in their entirety.

A cross-fostering experiment was incorporated into the initial reproductive toxicity study to determine whether the decreased pup survival resulted from in utero or lactational exposure. Pups that were cross-fostered to treated dams exhibited convulsions and excessive mortality, whereas pups that were cross-fostered to control dams had normal patterns of development and survival and no signs of convulsions. The results of this cross-fostering experiment suggest that exposure of pups to noviflumuron via lactation was responsible for the decreased survival, and that in utero exposure played little to no role in pup mortality.

In a subsequent two-generation dietary reproductive toxicity study, the high dose was lower than the high dose used in the one-generation reproductive toxicity study in order to ensure adequate pup survival. No adverse effects were observed in parental animals up to the highest dose tested. At the high dose, offspring survival was reduced after PND 4. Tonoclonic convulsions were observed between PND 7 and 16 in several litters at the high dose. Other high-dose offspring effects included reduced activity in F1 pups and reduced body weights and body weight gains in F1 and F2A litters from PND 7 to 21. The only treatment-related effect noted in offspring at the mid-dose level was the observation of tonoclonic convulsions in one F2A litter on one occasion, PND 14. It was noted in this study that the convulsions were more pronounced in the F2A litters than in the F1 litters. In the F1 pups, only single episodes of convulsions were observed. In the F2A pups, three litters exhibited convulsions on multiple occasions, and three of four dams with convulsing pups lost their entire litter between PND 8 and 14. Overall, there was evidence of sensitivity in the young in this study, as a serious endpoint (pup mortality) was observed in the absence of maternal toxicity.

With respect to reproductive toxicity, no effect on reproductive performance was observed in the P parental generation animals in the two-generation reproductive toxicity study. In the F1 generation, there was an apparent reduction in conception and fertility indices in the first mating of the F1 parental animals at all doses tested, resulting in a decrease in the number of litters and live F2A pups. However, following the second mating of the F1 parental animals, the conception and fertility indices for the low-dose animals were comparable to controls. When both matings of the F1 parental animals are considered, there was a consistent reduction in mating and fertility

indices and in the numbers of litters and live pups at the mid- and high-dose levels. There was also an increase in the F1 females that failed to produce a litter in either mating at the mid-dose level. At the mid- and high-dose levels, five and seven F1 females, respectively, were determined to be infertile, versus one F1 female in the control and low-dose groups. At the highest dose tested, consistent reductions in the conception index were observed in both matings of the F1 parental animals. In this study, the LOAEL for reproductive toxicity was established at the mid-dose level, which could be considered conservative given the following: (a) none of the reductions in reproductive indices were statistically significantly different from controls; (b) there was no impact on mean litter size at the mid-dose level; (c) over 70% of the matings at the mid-dose level resulted in a live litter with the value increasing to 80% in the second pairing of animals when animals were mated with proven animals of the opposite sex; and (d) the conception index was decreased at this dose level in the first mating only. In making this determination, consideration was given to Holson et al. (2009), who caution that the evaluation of fertility index in isolation is a poor predictor of reproductive system impairment, and that is it is essential to evaluate other interrelated endpoints, such as organ weights, macroscopic and microscopic tissue changes, estrous cycle data, and oocyte quantification. The reduced mating and fertility indices in the noviflumuron two-generation reproductive toxicity study were observed in the absence of any other effects on the reproductive system, including sperm and ovarian follicle counts, estrous cyclicity, and pathology of the tissues of the reproductive system.

The requirement for a short-term dermal toxicity study was waived for this registration petition for noviflumuron in consideration of the proposed use pattern as well as the fact that the endpoints of concern (impaired fertility and reduced pup survival) that have been identified following oral dosing with noviflumuron are not addressed in the typical design of a short-term dermal toxicity.

Results of the toxicology studies conducted on laboratory animals with noviflumuron and its associated manufacturing concentrate and end-use product, are summarized in Appendix I, Tables 2, 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. Noviflumuron is a new active ingredient pending registration for use in Canada. No human or domestic animal incidents involving the active ingredient noviflumuron have been reported to the PMRA and the applicant did not submit any additional data. In the United States, there was one reported minor incident involving noviflumuron.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to

threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the noviflumuron database contains the standard complement of required studies including developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats. In addition, a one-generation reproductive toxicity study in rats that included a cross-fostering component and a whole embryo culture teratology screen in rats were available.

With respect to potential prenatal and postnatal toxicity, no evidence of developmental toxicity was apparent in the rat or rabbit up to the limit dose of testing. Sensitivity of the young was evident in the two-generation reproductive toxicity study in rats. Convulsions occurred in offspring in that study at a dose level that did not elicit parental toxicity. In other studies, adult animals also exhibited convulsions but at higher doses, indicating sensitivity of the young for that endpoint. However, this effect is well characterized and NOAELs for the effect have been established in young and adult animals. Effects of a serious nature were also observed in the two-generation reproductive toxicity study. Reduced pup survival occurred at the highest dose level, a dose level that was not toxic to the parental animal. Impaired fertility occurred at the mid-dose level in the absence of other indications of systemic toxicity in parental animals. Impaired fertility is considered relevant within the context of the provisions of the *Pest Control Products Act*, as the ability to produce future generations could be compromised. However, the level of concern is tempered by the conservativism associated with the point of departure for this finding in the noviflumuron two-generation study as discussed previously.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well-characterized. Given the conservative approach to the establishment of the point of departure for reproductive toxicity, the *Pest Control Products Act* factor was reduced to 3-fold for exposure scenarios using the toxicological endpoint for impaired fertility from the two-generation reproductive toxicity study. Selection of this endpoint provides protection for the convulsions and reduced pup survival observed in the two-generation rat reproductive toxicity study. For all other exposure scenarios, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose

An acute reference dose (ARfD) was not required as there are no food uses associated with noviflumuron.

3.3 Acceptable Daily Intake

An acceptable daily intake (ADI) was not required as there are no food uses associated with noviflumuron.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to noviflumuron is characterized as short- to long-term in duration and by the dermal route. Inhalation exposure was not calculated as the vapour pressure of noviflumuron at 2.2×10^{-10} Pa (20°C) indicates it is non-volatile in outdoor environments. Also, the formulation, which includes a binding agent, reduces the likelihood of any dust-off.

For short- to long-term dermal exposure scenarios, the NOAEL of 0.5 mg/kg bw/day for reproductive toxicity from the two-generation reproductive toxicity study in rats was selected for use in risk assessment. Impaired fertility occurred at the LOAEL of 5 mg/kg bw/day.

The target margin of exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The concerns outlined in the *Pest Control Products Act* Hazard Characterization section regarding this endpoint are relevant to the worker population. For these reasons, an additional factor of 3-fold was applied to these risk assessments to protect workers of child-bearing age.

The selected endpoint and target MOE provide margins of 3000 and 300, respectively, to the NOAELs for reduced pup survival and convulsions in offspring observed in the two-generation rat reproductive toxicity study. The endpoint of reduced fertility and target MOE provide margins of 500 or greater to the NOAELs for each of the observed tumour types.

Cancer Assessment

In the oncogenicity studies conducted with noviflumuron, increased incidences of hepatocellular adenomas were observed in male and female mice and in male rats, while increased incidences of uterine stromal polyps were observed in female rats. However, concern for these findings was lessened by the fact that there was no evidence of genotoxicity in any of the in vivo or in vitro assays conducted with noviflumuron, all of the tumour types are benign in nature with no evidence of progression to malignancy, and the increase in tumour response generally occurred at high doses, some of which exceeded the point of saturation of absorption or were considered to be excessive. For these reasons, a threshold-based approach was deemed appropriate for the cancer risk assessment. The selected toxicological endpoint and target MOE provide sufficient margins to each of these tumour types.

3.4.1.1 Dermal Absorption

Penetration of the stratum corneum is dependent upon molecular weight or size where chemicals with high molecular weights diffuse more slowly thereby decreasing dermal absorption. The molecular weight of noviflumuron is 529.15 g/mol and is considered large, thus is considered as a potential impediment to absorption.

The solubility of a chemical in polar and non-polar solvents is often the rate limiting step in the penetration of skin. Noviflumuron's low solubility in water at 0.194 mg/L (at 20°C) can hinder absorption as it may not be able to dissolve in the hydrophilic epidermis.

Maximum absorption is often associated with values of log K_{ow} between 1 and 2 with the limit approaching 3.5. Above this, compounds are likely to remain in the stratum corneum. Noviflumuron has a log K_{ow} value of 4.94 which would suggest it would have difficulty passing through the inter-cellular space since it may become bound with the lipophilic layer.

The physical state of the chemical also has an effect on dermal absorption. A liquid will dissolve into the skin more easily than a solid, as a liquid does not have to undergo a change of state. Recruit HD would likely have a lower dermal absorption value because of its solid state.

Generally, large, charged, highly lipid or water insoluble chemicals are not good candidates for dermal absorption. From the physical and chemical properties of noviflumuron, it is possible to conclude that it is not likely to have a high dermal absorption value. As such, it is possible to reduce the dermal absorption value from the Agency default of 100% to 50%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Exposure and Risk Assessment

There is potential for exposure to noviflumuron during installation and monitoring of Recruit HD Termite Bait. As chemical-specific data for assessing human exposure during pesticide handling activities were not submitted, dermal exposure estimates for Pest Control Operators (PCOs) are generated from PHED (version 1.1) using the Granular Dispersion by Hand Scenario 15b. The exposure estimates are based on PCOs wearing a long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves. Given the end-use product is formulated with a cellulose polymer binder, the granular bait is likely to overestimate exposure, particularly when the unit exposure for the entire body is used. As such, to quantitatively estimate exposure during handling, only the hand unit exposure value is used. Also, Recruit HD Bait is in the shape of a cylinder, approximately 3.8 cm in diameter, so the PCO would only be exposed to the noviflumuron on the outer most surface. The amount of active ingredient available was therefore reduced accordingly.

Dow AgroSciences indicated that approximately 20–25 baits are used per home and that a PCO can treat up to 3 homes per day. As such, exposure and risk was calculated assuming a maximum of 75 baits per day.

Dermal exposure was estimated by combining the dermal unit exposure value with the amount of product handled per day and the dermal absorption value. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates are compared to the dermal toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 300. The dermal MOE for hand exposure exceeded the target MOE when up to 75 baits are installed per day (see Appendix I, Table 6).

3.4.2.2 Postapplication Worker Exposure and Risk

PCOs will also be exposed during monitoring and servicing of the bait stations. During this process, older bait stations will be removed and replaced, if necessary. Exposure during this process is not expected to be greater than that during installation and it is not expected that a greater number of stations will be serviced than installed per day.

3.4.3 Residential Exposure and Risk Assessment

Residential and bystander exposure is expected to be negligible as the Recruit HD Termite Bait is in solid form and applied into the sub-surface. A locking mechanism is part of the cap of the Sentricon Colony Elimination System bait station which protects against tampering particularly from small children. Because of this, the bait is restricted for installation with the Sentricon Colony Elimination System bait station only.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Noviflumuron is used in a commercial bait system to protect structures from termite infestations. Very little noviflumuron is expected to reach the environment when it is used as a solid bait station to control termite activity.

Data on the fate and behaviour of noviflumuron are summarised in Appendix I, Table 7.

Based on its physical and chemical properties, noviflumuron is sparingly soluble in water. Volatilization from moist soil or water surfaces is unlikely to be a significant route of dissipation of noviflumuron in the environment. The log K_{ow} value of 4.9 indicates that noviflumuron has the potential to bioaccumulate; however, because environmental exposure is expected to be minimal, bioaccumulation is not expected to be of concern.

If noviflumuron enters the environment, it is expected to be persistent. In soil, noviflumuron transforms slowly through biotransformation with half-lives ranging from 202 to 399 days. The major transformation product is the XDE-007 amine. In aquatic environments, noviflumuron is stable to hydrolysis under most environmentally relevant conditions. Hydrolysis can occur, however, under alkaline conditions (half-life of 19 days, pH 9). Major hydrolysis transformation products are XDE-007 urea and XDE-007 amine (pH 9).

Mobility studies on European and American soils indicate that noviflumuron is immobile in all soil types. These studies and the limited use-pattern indicate that noviflumuron is unlikely to leach to groundwater.

4.2 Environmental Risk Characterization

A quantitative environmental risk assessment was not conducted due to the very limited environmental exposure.

5.0 Value

In Canada, the management of termites has traditionally involved the application of insecticides containing permethrin (mode of action group 3), chlorantraniliprole (mode of action group 28) or chlorfenapyr (mode of action group 13) to soil surrounding the structure. These products kill only those termites which come in contact with the insecticide treated soil. The structural pest control industry has indicated that there is a need for bait against subterranean termites which would target the entire colony.

Recruit HD Termite Bait represents the first termite bait in Canada that targets the colonies of subterranean termites. It consists of attractive bait and the insect growth regulator noviflumuron. Noviflumuron represents a new mode of action to control termites. As the bait becomes distributed throughout the colony, it prevents juveniles from developing into adults resulting in elimination of the colony. Since it is applied in a bait station, less insecticide is applied compared to traditional soil applied termiticides. It is to be used as part of an integrated pest management approach to termite control. Monitoring of the bait stations is essential for establishing locations of termite activity and ensuring that there is a continuous supply of bait.

Efficacy data and history of use in successful subterranean termite programs from countries, such as the United States, demonstrated noviflumuron baits is effective in controlling subterranean termites.

5.1 Supported Uses

Recruit HD Termite Bait is to be applied within Sentricon Colony Elimination System bait stations around structures, as well as landscape plantings and trees, to eliminate colonies of subterranean termites.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity, and toxic as defined by the *Canadian Environmental Protection Act*].

From a screening perspective, the persistence and bioaccumulation criteria for TSMP may be met, however, exposure of novaluron to the environment is expected to be very limited when novaluron is applied as a termite bait within the Sentricon Colony Elimination System bait station. Traditional termite control products are applied directly to the soil to create a chemical barrier between the structure and termites. The use of novaluron as a termite bait may reduce the amount of other termiticides used, thereby reducing the potential for exposure of these products to the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical product and formulants, and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[7] The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations, including DIR99-03 and DIR2006-02,[9] and takes into consideration the Ozone-Depleting Substances Regulations, 1998, of the *Canadian Environmental Protection Act* (in other words, substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- The novaluron end-use product, Recruit HD Termite Bait, contains the preservative, 1,2-benzisothiazoline-3-one, which contains low levels of polychlorinated dibenzodioxins and furans. The use of this preservative in pest control products at a maximum of 0.1% was reassessed by PMRA in 2012 and found to be acceptable because dioxin and furan levels are low/being managed as outlined in the PMRA Regulatory Directive DIR99-03 on implementation of TSMP. Thus, the Agency position is that no further action be taken.

- Technical grade novaluron does not contain any other formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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7 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2640–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1641–1643: *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern*.

8 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

9 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for novaluron is adequate to define the majority of toxic effects that may result from exposure. In short- and long-term studies with adult animals, the targets of toxicity were the liver, kidney, adrenal gland, skin, testes, bone marrow, and lung. Novaluron did not demonstrate evidence of genotoxicity, but there was evidence of oncogenicity in rats and mice after longer-term dosing. There was no developmental toxicity resulting from in utero exposure to novaluron. Convulsions and reduced survival occurred in neonates exposed to novaluron during the period of lactation. These effects occurred in the absence of parental toxicity, thus demonstrating increased susceptibility of the young in the rat. Impaired fertility was also evident in female rats. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

PCOs handling Recruit HD Termite Bait are not expected to be exposed to levels of novaluron that will result in an unacceptable risk when it is used according to label directions. The personal protective equipment of a long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves and safety glasses on the product label is adequate to protect PCOs.

Residential and bystander exposure is not expected to occur when Recruit HD Termite Bait is used according to label directions, which includes restricting the use only with the Sentricon Colony Elimination System bait station which has a locking cap mechanism.

7.2 Environmental Risk

Very limited environmental exposure is expected under proposed use pattern for Recruit HD Termite Bait, therefore, potential risks to the environment are expected to be minimal.

7.3 Value

Recruit HD Termite Bait, a combination of attractive bait and the insect growth regulator novaluron, is the first bait in Canada that eliminates colonies of subterranean termites by preventing juveniles from developing into adults. The use of a bait to control termites represents a new method in managing this pest in Canada and the structural pest control industry has identified such a need in termite management programs. Recruit HD Termite Bait targets the colony and results in application of less insecticide compared to traditional soil treatments for termites. Novaluron represents a new mode of action against subterranean termites and the development of resistance is unlikely.

9.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Novaluron Technical Insecticide, Novaluron 10% Manufacturing Concentrate and Recruit HD Termite Bait, containing the technical grade active ingredient Novaluron, to control colonies of subterranean termites to protect structures from termite damage.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	female
↑	increase
↓	decrease
%	percent
>	greater than
≥	greater than or equal to
λ	wavelength
ε	emittance
°C	Celsius
abs.	absolute
AD	absorbed dose
a.i.	active ingredient
ADI	acceptable daily intake
ALK	alkaline phosphatase
ALS	acetolactate synthase
AST	aspartate aminotransferase
ARfD	acute reference dose
AUC	area under the curve
atm	atmosphere
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CAS	Chemical Abstracts Service
Cmax	maximum plasma concentration
cm	centimetres
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ER_{25}	effective rate for 25% of the population
F1	first generation
F2	second generation
fc	food consumption
g	gram
GD	gestation day
GI	gastrointestinal
ha	hectare(s)
HCT	hematocrit
HDT	highest dose tested
Hg	mercury

HGB	hemoglobin
HPLC	high performance liquid chromatography
HPLC/MS/MS	High-Performance Liquid Chromatography with tandem Mass Spectrometry
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg a.i.	Kilogram active ingredient
kg bw	Kilograms bodyweight
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LGLL	large granular lymphocytic leukemia
1/n	exponent for the Freundlich isotherm
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
MAS	maximum average score
MCV	mean corpuscular volume
MIS	maximum irritation score
mg	milligram
mL	millilitre
mg a.i.	Milligram active ingredient
mg/kg bw/day	Milligram per kilogram body weight per day
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MS	mass spectrometry
NA	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
Pa	Pascals
PBI	plantback interval
PCO	Pest Control Operator
PE	pellets
pH	measure of the acidity or basicity of an aqueous solution
PHED	Pesticide Handlers Exposure Database

PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
RBC	red blood cell count
rel.	relative
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
Tmax	time to maximum plasma concentration
UAN	urea ammonium nitrate
UF	uncertainty factor
µg	micrograms
µg/kg a.i.	Micrograms per kilogram active ingredient
US	United States
UV	ultraviolet
v/v	volume per volume dilution
WBC	white blood cell count
wt	weight
XDE-007	noviflumuron

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	NA	Active	HPLC/MS/MS	0.01 ppm	PMRA # 2463360
Sediment	NA	Active	HPLC/MS/MS	0.01 ppm	PMRA # 2643360

Table 2 Toxicity Profile of Recruit HD Termite Bait Containing Noviflumuron
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral Acute dermal Acute inhalation Dermal irritation Eye irritation Dermal sensitization PMRA 2277921	Waiver request granted based on the very low acute toxicity and low concentration (0.5%) of the active ingredient and the low toxicity of the inert co-formulants (cellulose matrix).

Table 3 Toxicity Profile of Noviflumuron 50% Manufacturing Concentrate
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.)

Study Type/Animal/PMRA #	Study Results
Acute oral (standard test) Rat (Fischer 344) PMRA 2277876	Low Toxicity LD_{50} > 5000 mg/kg bw Clinical signs were limited to perineal soiling with urine.
Acute dermal Rat (Fischer 344) PMRA 2277877	Low Toxicity LD_{50} > 5000 mg/kg bw Clinical signs included perineal soiling with urine, periocular soiling, perinasal soiling, and lacrimation.

Study Type/Animal/PMRA #	Study Results
Acute inhalation Rat (Fischer 344) PMRA 2277878	Low Toxicity LC_{50} > 0.92 mg/L (maximum obtainable concentration) Clinical signs included wet brown material around the nose immediately following exposure, followed by unkempt appearance, dried red material on the facial area and/or around the eyes, brown material around the nose and/or eye during the post-exposure observation period.
Dermal irritation Rabbit (New Zealand White) PMRA 2277880	Non-irritating All dermal scores were zero.
Eye irritation Rabbit (New Zealand White) PMRA 2277879	Non-irritating All ocular scores were zero.
Dermal sensitization (Buehler) Guinea pig (Hartley albino) PMRA 2277881	Negative All dermal scores were zero.

Table 4 Toxicity Profile of Technical Noviflumuron

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.)

Study Type/Animal/PMRA #	Study Results
Acute oral (standard test) Rat (Fischer 344) PMRA 2277802	Low Toxicity LD_{50} > 5000 mg/kg bw Clinical signs were limited to perineal fecal soiling.
Acute dermal	Low Toxicity

Study Type/Animal/PMRA #	Study Results
Rabbit (New Zealand White) PMRA 2277805	LD_{50} > 5000 mg/kg bw Dermal signs included thickened skin at the dermal test site. Clinical signs were limited to perineal fecal soiling.
Acute inhalation Rat (Fischer 344) PMRA 2277806	Low Toxicity LC_{50} > 5.24 mg/L Clinical signs included perineal soiling (urine and/or fecal), abdominal soiling (fecal), and extensive body soiling (urine and fecal).
Dermal irritation Rabbit (New Zealand White) PMRA 2277808	Non-irritating All dermal scores were zero.
Eye irritation Rabbit (New Zealand White) PMRA 2277807	Minimally Irritating MAS = 0.4/110 MIS = 7.3 /110 (at 1 hour) All scores were zero by 48 hours post-instillation.
Dermal sensitization (Buehler) Guinea pig (Hartley albino) PMRA 2277812	Negative No dermal reactions were observed.
Dermal sensitization (Maximization) Guinea pig (Hartley albino) PMRA 2277810	Negative Dermal scores were similar between the test and control groups after each challenge application.
28-day dermal PMRA 2277801; 2277813	The requirement for a short-term dermal toxicity study was waived for this registration petition for noviflumuron in consideration of the proposed use pattern as well as the fact that the endpoints of concern (i.e., impaired fertility and reduced pup survival) that have been identified following oral dosing with noviflumuron are not addressed in the typical design of a short-term dermal toxicity.
28-day oral (dietary) Mouse (CD-1) PMRA 2277816	NOAEL = 10.8/11.2 mg/kg bw/day (♂/♀) LOAEL = 110/113 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ platelets, ↑ cholesterol, ↑ liver wt.
28-day oral (dietary)	NOAEL = 101/105 mg/kg bw/day (♂/♀) LOAEL = 513/521 mg/kg bw/day (♂/♀)

Study Type/Animal/PMRA #	Study Results
Rat (Fischer 344) PMRA 2277819	Effects at the LOAEL: ↑ liver wt, ↑ abs. kidney wt, ↑ ALK, ↓ glucose, ↑ cholesterol; centrilobular hepatocellular hypertrophy (♀).
90-day oral (dietary) Rat (Fischer 344) PMRA 2495523	NOAEL = 11.0/10.6 mg/kg bw/day (♂/♀) LOAEL = 110/105 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw, ↓ bwg, ↑ ALK, ↓ AST, ↓ glucose, ↑ cholesterol, ↑ liver wt, ↑ rel. kidney wt, hepatocellular hypertrophy with altered tinctorial properties [↑ eosinophilic staining of the cytoplasm]; ↑ prothrombin time, ↑ protein (♂); ↑ adrenal wt (♀).
90-day oral (dietary) – dose range-finding study for the two-generation reproductive toxicity study Rat (Sprague Dawley) PMRA 2495522	NOAEL and LOAEL not established as study was considered supplemental Effects at 10 mg/kg bw/day included hepatocellular vacuolization consistent with fatty change (very slight in 2/8 rats at this dose), hypertrophy of the zona fasciculata of the adrenal gland (very slight in 3/8 rats at this dose) (♀).
90-day oral (dietary) Dog (Beagle) PMRA 2277814	NOAEL = 0.9/1.1 mg/kg bw/day (♂/♀) LOAEL = 115/113 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ RBC, ↑ MCV, hyperplasia of erythroid cells of the bone marrow, ↑ platelets; ↓ HGB, ↓ HCT, ↑ kidney wt, ↑ rel. liver wt (♂).
One-year oral (dietary) Dog (Beagle) PMRA 2495524	NOAEL = 9.3/8.7 mg/kg bw/day (♂/♀) LOAEL = 69/70 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ incidence of polychromasia, hyperplasia of erythroid cells of the bone marrow, ↑ WBC, platelets; ↑ incidence of soft feces, ↑ MCV, ↑ cholesterol (♂); ↑ reticulocytes (♀).
Two-year combined chronic toxicity / oncogenicity (dietary) Rat (Fischer 344) PMRA 2277821, 2495525	NOAEL = 1.0 mg/kg bw/day (♂/♀) LOAEL = 79/76 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw (slight), ↓ bwg, ↑ ALK, ↓ AST, ↑ cholesterol, ↑ liver wt, lung foci, chronic inflammation of the lung, hepatocellular hypertrophy, hyperkeratosis & inflammation of the hair follicles of the tail; skin papules & pustules on the tail, ↑ prothrombin time, ↑ protein, ↑ BUN, ↑ kidney wt, ↑ testes wt, ↓ epididymal wt, ↓ spleen wt (↓ incidence LGLL), ↑ basophilic foci of cellular alteration in the liver, hyperplasia and mineralization of the renal pelvic epithelium, bilateral aspermia, larger testicular interstitial cell tumors (♂); ↓ motor activity, urine soiling, ↓ basophilic foci of cellular alteration in the liver, ↑ adrenal gland wt, uterine mass/nodule (♀). Neoplastic lesions: ↑ incidence of hepatocellular adenomas (♂); ↑ incidence of uterine stromal polyps (♀). Evidence of oncogenicity.

Study Type/Animal/PMRA #	Study Results
18-month oncogenicity (dietary) Mouse (CD-1) PMRA 2277823	NOAEL = 3.0/0.5 mg/kg bw/day (♂/♀) LOAEL = 30/31 mg/kg bw/day (♂/♀) Effects at the LOAEL: inflammation of lung (♂), ↑ liver wt, aggregates of alveolar macrophages (♀). Effects at the next higher dose level of 100 mg/kg bw/day: tonoclonic convulsions after 8 months of dosing, ↑ mortality, hepatocellular hypertrophy (♀). Neoplastic lesions: ↑ incidence of hepatocellular adenomas. Evidence of oncogenicity in ♂ Evidence of oncogenicity in ♀ at a dose that exceeded the maximum tolerated dose
One-generation reproduction with cross-fostering (dietary) Rat (Sprague-Dawley) PMRA 2495526	NOAEL and LOAEL not established as study was considered supplemental Effects in parental animals at 100 mg/kg bw/day included tonoclonic convulsions weeks 11 to 15, ↓ fc, ↓ bw (♂); ↓ bw & bwg during gestation and lactation (♀). Reproductive effects at 100 mg/kg bw/day included ↓ number of live born pups, ↑ stillbirths. Effects in offspring at 100 mg/kg bw/day included ↓ pup survival (complete loss of 23/24 litters by PND 21; most deaths between PND 4 and 14), tonoclonic convulsions, pale skin, stomach void of milk, placental tissue attached, thin appearance, cold to touch, ↓ pup bw PND 7 & 14. Of the 13 dams switched to control diet during lactation, 12 lost their entire litters. Pups cross-fostered to treated lactating dams had convulsions and excessive mortality with total litter loss in 7/8 litters, whereas pups cross-fostered to control dams had normal patterns of development and survival, and no signs of convulsion. These results suggest that exposure to novaluron via lactation was responsible for decreased pup survival and that gestational exposure played little to no role.
Two-generation reproduction (dietary) Rat (Sprague Dawley) PMRA 2277828	Parental NOAEL = 25 mg/kg bw/day (highest dose tested) Parental LOAEL not established as no adverse effects were observed Reproductive NOAEL = 0.5 mg/kg bw/day Reproductive LOAEL = 5 mg/kg bw/day Effects at the reproductive LOAEL: ↓ mating and fertility indices in both matings of F1 parental animals, ↓ conception indices in first mating of F1

Study Type/Animal/PMRA #	Study Results
	parental animals, ↓ numbers of litters and live pups in both matings of F1 parental animals, ↑ number of infertile F1 females (♂). Offspring NOAEL = 0.5 mg/kg bw/day Offspring LOAEL = 5 mg/kg bw/day Effects at the offspring LOAEL: tonoclonic convulsions in one F2A litter on PND 14. Effects in offspring at the next higher dose level of 25 mg/kg bw/day: ↓ pup survival after PND 4 F1 and F2A, complete litter losses (2 F1 litters, 3 F2A litters), tonoclonic convulsions PND 7 to 16 (5 F1 litter, 4 F2A litters), decreased activity F1, ↓ bw PND 7-21 F1 and F2A, ↓ bwg F1 and F2A. Serious endpoint (reduced pup survival) in the absence of maternal toxicity
Developmental toxicity (gavage) Rat (Sprague Dawley) PMRA 2277831	Maternal NOAEL = 1000 mg/kg bw/day (highest dose tested) Maternal LOAEL not established as no adverse effects were observed Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL not established as no adverse effects were observed No evidence of sensitivity of the young
Developmental toxicity (gavage) Rabbit (New Zealand White) PMRA 2277833	Maternal NOAEL = 1000 mg/kg bw/day (highest dose tested) Maternal LOAEL not established as no adverse effects were observed Developmental NOAEL = 1000 mg/kg bw/day Developmental LOAEL not established as no adverse effects were observed No evidence of sensitivity of the young
Whole embryo culture teratology screen (gavage) Rat (strain not stated) PMRA 2495531	Rat conceptuses from untreated, time-mated female rats were explanted on GD 9 and were cultured for 48 hours in serum collected from non-pregnant female rats that had been dosed with novaluron via gavage for 3 days. No effects on body weight or clinical observations of serum donors. Embryo viability and growth parameters at 1000 mg/kg bw were similar or slightly greater than those of the control embryos. There were no treatment-related morphological abnormalities in the embryos. The test material was considered negative for teratogenic potential in this screening test. Study considered supplemental

Study Type/ Animal/ PMRA #	Study Results
Bacterial reverse gene mutation *S. typhimurium* TA98, TA100, TA1535, TA1537, E. coli WP2uvrA PMRA 2277635	Negative Tested up to precipitating concentrations
In vitro forward mutation assay in mammalian cells Chinese hamster ovary cells PMRA 2277636	Negative Tested up to precipitating concentrations
In vitro chromosomal aberration assay (screening assay) Rat lymphocytes PMRA 2095526	Negative Tested up to precipitating concentrations Study considered supplemental
In vitro chromosomal aberration assay Rat lymphocytes PMRA 2095527	Negative Tested up to precipitating concentrations
In vivo micronucleus assay Mouse (CD-1) PMRA 2277640	Negative Tested up to the limit dose
Limited toxicokinetics (gavage) Rat (Fischer 344) ^{14}C-XDE-007, uniformly radiolabelled on the fluoroalkilomethoxyl ring PMRA 2277642	Absorption was rapid, with quantifiable levels of radioactivity in plasma within 15 minutes of dosing. T_{max} was between 5 and 6 hours post-dosing. Neither C_{max} nor AUC were proportional to dose. For an approximately 10-fold increase in dose between the low and mid doses, C_{max} and AUC increased approximately 6 to 7-fold. For an approximate increase of 25-fold between the low and high doses, C_{max} and AUC increased approximately 7 to 9-fold. At 72 hours post-dose, approximately 1 to 5% of the administered dose was recovered in urine and 93 to 98% of the administered dose was recovered in feces. The amount of radioactivity recovered in urine was higher for females than for males, and decreased with increasing dose. Approximately 54% to 69% of the total radioactivity excreted in urine was recovered within 24 hours of

Study Type/ Material PMRA #	Study Results
	dosing, and 91% to 98% of the total radioactivity excreted in urine was recovered within 48 hours of dosing. The rate of clearance from urine was 5 to 6 mL/hour. The amount of radioactivity recovered in feces was higher for females than for males, and increased with increasing dose. In males, fecal elimination of radioactivity occurred rapidly, with 88% to 95% of the total excreted radioactivity recovered within 24 hours. In females, 58% to 77% of the eliminated radioactivity was recovered within 24 hours post-dosing and 96% within 48 hours. The half-life of elimination from plasma ranged from 52 to 63 hours. Radioactivity was still detected in plasma at 72 hours post-dosing. No parent compound was detected in urine. Two circulating urinary metabolites, identified as the glucuronide conjugate of hexafluoropropoxy-fluoroalkiloxyaniline and the mercapturic acid conjugate of the parent compound, comprised 35% of the urinary excreted radioactivity. A third urinary metabolite was identified as the sulfate conjugate of hexafluoropropoxy-fluoroalkiloxyaniline and comprised 65% of the urinary excreted radioactivity.
Toxicokinetics (gavage) Rat (Fischer 344) PMRA #: 2495529 [14C-XDE-007], uniformly radiolabelled on the fluoroalkiloxyphenyl ring or the difluorobenzoyl ring	The amount absorbed was 81% to 96% of the AD following a single low dose, 95% of the AD following multiple low doses, and only 2% to 9% of the AD following a single high dose (7 slightly +). When considering the excretion of radioactivity via the feces of animals dosed intravenously with the low dose of the fluoroalkiloxyphenyl ring-label (40% in males and 41% in females), the estimated absorption following the administration of a single low oral dose is likely higher than the above-reported values. Urinary excretion was 10-16% of the AD (7+) for all low dose groups with the fluoroalkiloxyphenyl radiolabel. With the difluorobenzoyl radiolabel, 37% of the AD was detected in urine. Only 1% of the AD was in urine after a single high dose. Urinary elimination was relatively slow (>80% of the urinary radioactivity eliminated 96 and 72 hours after dosing with low and high dose, respectively). The elimination of radioactivity in urine was biphasic, with a more rapid early phase (half-life of 20 to 36 hours) and a slower late phase (half-life of 62 to 110 hours). Radioactivity in feces accounted for 51% to 64% of the AD following low doses and 90% to 96% of the AD following a single high dose of the fluoroalkiloxyphenyl ring-label. Following a low dose of the difluorobenzoyl ring-label, 36% to 41% of the AD was detected in feces. Biliary elimination accounted for 53% to 60% of the AD following IV dosing. Fecal elimination was rapid at the high dose (96% of fecal radioactivity excreted within 24 hours). For the low dose groups, fecal elimination was slower (<80% of fecal radioactivity excreted from 72 and 120 hours). Following a single or multiple oral low doses, 17% to 29% of the AD

Study Type/Animal/PMRA #	Study Results
	remained in tissues up to 7 days post-dosing (<1% to 17% of the AD was detected in the residual carcass, 2% to 5% of the AD was detected in the skin, and 2% to 5% of the AD in the GI tract). Of the remaining tissues, the liver, kidney, fat and uterus contained the next highest residue levels. Following the oral administration of a single high dose of ^{14}C-XDE-007, only approximately 1% of the AD remained in tissues at 7 days post-dosing, with highest levels in the GI tract, carcass and skin. When normalized for tissue weight, the highest levels of radioactivity were detected in the fat, ovaries, adrenal gland, skin, liver and kidney. The ratio between tissue levels at the two dose levels was 1 to 21/840 (month), 1 to 6/840 higher than the low dose), well below the 100/840 difference between the two doses.
Toxicokinetics (gavage) (continued) Rat (Hsd:Sprague Dawley) PMRA #: 2469920 ^{14}C-XDE-007, uniformly radiolabelled on the fluorodichlorophenyl ring or the difluorobenzoyl ring	Most of the radioactivity recovered in feces was identified as unchanged XDE-007 (>95% of the AD with the single and low dose of the difluorobenzoyl ring-label; 67% to 94% of the AD with the single or multiple oral low doses of the fluorodichlorophenyl ring-label; 35% to 36% following the 56 low dose of the fluorodichlorophenyl ring-label; 90% to 96% of the AD with the single high dose of the of the fluorodichlorophenyl ring-label). Four minor metabolites were identified in feces, but only one was characterized. The fecal metabolite (2% to 9% of the AD following low doses of the fluorodichlorophenyl ring-label) was determined to be a decarbon analog of parent compound, arising either by metabolic decarbonation or more probably as an impurity of the radiolabelled test material. Four urinary metabolites were characterized. The major urinary metabolites represented cleavage of the aryl urea moiety. The urinary metabolites arising from the difluorobenzoyl ring-label were difluorobenzoic acid (12% of the AD) and the corresponding glycine (hippuric acid) conjugate (4% of the AD). The fluorodichlorophenyl ring-labelled metabolites arose via hydroxylation (2% to 6% of the AD in feces following single or multiple oral low doses), followed by conjugation with glucuronic acid (2% to 8% of the AD in urine) following single or multiple oral low doses) and sulfate (6% to 17% of the AD in urine following single or multiple oral low doses; 1.1% of the AD in urine following a single oral high dose). XDE-007 is either excreted unchanged or metabolized via cleavage of the aryl urea moiety followed by conjugation with glycine and excretion via urine.
Special toxicokinetics study to determine the time-course, distribution and localization of radioactivity within different regions of the brain Rat (Hsd:Sprague Dawley) PMRA #: 2469930	Following a single dose, the level of radioactivity in the brain, plasma, and whole blood including red blood cells declined by 17%, 64% and 70%, respectively, between 7 and 24 hours post-dosing. The radioactivity in the brain following a single dose was below the level that could be used for autoradiographic localization and thus no further assessment of this group was conducted. Following repeated doses, a total of 17%, 26%, and 13% of the AD

Study Type/Animal/PMRA #	Study Results
^{14}C-XDE-007; uniformly radiolabelled on the fluorodichlorophenyl ring	remained in tissues, carcass and the GI tract (including contents) combined at 3, 24 and 120 hours after the final radiolabelled dose, respectively. The daily urinary excretion of radioactivity was 3% to 4% of the remaining dose in the body during the dosing period, and decreased to 2% per day during the post-dosing period. Daily urinary elimination was slightly higher during the first five days of dosing compared to the last five days. A total of 12% of the AD was eliminated in the urine over the course of the 10-day dosing period and up to 7 days post-dosing. The daily fecal excretion of radioactivity ranged from 20% to 32% of the remaining dose in the body during the first four days of dosing, and then declined to 15% to19% of the body burden during the last six days of dosing. This amount declined even further during the post-dosing period to 6% to 8% of the body burden. A total of 63% of the AD was eliminated in the feces over the course of the 10-day dosing period and up to 7 days post-dosing. The decrease in urinary and fecal elimination with successive doses may be due to the increase in total body burden of nearly 5-fold between the first and last doses, and the fact that a steady stated of elimination was not reached during the dosing period. The distribution of the absorbed dose was in the order of fat >> adrenal gland ≥ skin > ovaries followed by spleen and liver. The radioactivity detected in the brain was low even after multiple (10 daily) doses (0.007% of the administered dose) and was only 3-fold higher than the level detected after a single dose. The distribution of the radioactivity within brain was focal and exclusively localized in blood vessels on the surface of the brain in the choroid plexus of the ventricles; none of the XDE-007 derived radioactivity crossed the blood brain barrier.

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Noviflumuron

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short- to long-term dermal[2]	Two-generation reproductive toxicity study in rats (dietary)	NOAEL for reproductive toxicity = 0.5 mg/kg bw/day, based on reduced fertility in the F1 generation	300
Cancer	Evidence of liver tumours in rats and mice and uterine stromal polyps in rats. The endpoint selected for non-cancer risk assessment is protective of any residual concerns regarding the oncogenic potential of noviflumuron.		

[1] MOE refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 50% was used in a route-to-route extrapolation.

Table 6 Dermal MOEs for a PCO Installing Recruit HD Termite Bait

Number of Bait Stations per Day [1]	Amount Handled per Day (kg a.i./day) [2]	PHED Granular Bait (Hand Only) (µg/kg a.i. handled) [3]	Hand Dermal Exposure (mg/kg bw/day) [4]	Dermal MOE [5]
25	0.00853	7978	0.000425	1180
75	0.0256		0.00128	392

[1] 25 stations per day is the maximum per dwelling and assumes a PCO can treat a maximum of 3 homes per day.
[2] Amount Handled per Day (kg a.i./day) = Number of Bait Stations per day (stations/day) × Rate (341 mg a.i./station) × Conversion Factor (kg/1000000 mg)
[3] PHED Scenario 15b: Granular Bait Dispensed by Hand (glove data only)
[4] Hand Dermal Exposure (mg/kg bw/day) = PHED (µg/kg a.i. handled) × Amount Handled per Day (kg a.i. handled/day) × Dermal Absorption (50%) × Conversion Factor (mg/1000 µg) ÷ 80 kg bw
[5] Dermal MOE = NOAEL of 0.5 mg/kg bw/day ÷ Hand Dermal Exposure (mg/kg bw/day); Target MOE = 300

Table 7 Fate and Behaviour in the Environment

Study type	Test material	Study conditions	Value or Endpoint	Interpretation	Major transformation products	References (PMRA #)
Abiotic transformation						
Hydrolysis	XDE-007	7 d, pH 5, 7 and 9, at 25°C	Stable @ pH 5 and 7; $t_{1/2}$ @ pH 9 = 19 days	Not a major route of transformation	pH 5 and 7: NA pH 9: XDE-007 urea and XDE-007 amine	2463548
Biotransformation						
Soil - aerobic	XDE-007	365 d, three soils, pH 5.2-7.5, %OC 0.8-4.2	DT_{50} = 202 to 399 d	Persistent	XDE-007 amine, CO_2	2463549
Mobility						
Adsorption/ desorption	XDE-007	Eight soils (pH 4.7-7.9, %OC 1.2-2.3)	K_{oc} = 32162 to 469335	Immobile	NA	2463550

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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2277796	2001, 5-Batch Analysis for XDE-007 Technical, DACO: 2.13.3 CBI
2277797	2001, Group B - Physical/Chemical Properties of XDE-007, DACO: 2.14,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9 CBI
2277798	2013, Sample of Analytical Standards, Noviflumuron Technical Insecticide, DACO: 2.15
2277800	2001, Group A: XDE-007 Technical Active Ingredient: Product Identity and Composition, Description of Materials used to Produce the Product, Description of the Production Process, Description of the Formulation Process, Discussion of Formation of Impurities
2277870	2013, Product Identification, Noviflumuron 50% Manufacturing Concentrate, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4 CBI
2277871	2001, Group A-Product Identity, Composition, and Analysis for GF-366; A Manufacturing Use Product Containing 50 Wt% XDE-007, DACO: 3.2.1,3.2.2,3.3.1,3.4.1,3.5.4 CBI
2277872	2001, Group B: Determination of Color, Physical State, Odor, Oxidizing and Reducing Action, Flammability, Explodability, pH, Viscosity and Density of GF-366, Manufacturing Concentrate Containing XDE-007, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.15,3.5.
2277873	2013, Storage Stability and Corrosion Characteristics, DACO: 3.5.10,3.5.14 CBI
2277914	2013, Product Identification, Recruit HD Termite Bait, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4 CBI
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2277917 2012, Accelerated Storage Stability of GF-2024 in Glass, DACO: 3.5.10 CBI

2277918 2012, Storage Stability and Package Corrosion Characteristics of GF-2024; One-Year Ambient Study, DACO: 3.5.10,3.5.14,3.5.5 CBI

2463360 2014, Determination of Residues of Noviflumuron in Soil and Sediment by Liquid Chromatography with Tandem Mass Spectrometry Detection, CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2277876	2001, GF-366: acute oral toxicity study in fischer 344 rats, DACO: 4.6.1
2277877	2001, GF-366: acute dermal toxicity study in fischer 344 rats, DACO: 4.6.2
2277878	2001, GF-366: Acute Inhalation Toxicity Study in the Fischer 344 Rat, DACO: 4.6.3
2277879	2001, GF-366: acute eye irritation study in new zealand white rabbits, DACO: 4.6.4
2277880	2001, GF-366: acute dermal irritation study in new zealand white rabbits, DACO: 4.6.5
2277881	2001, GF-366: a dermal sensitization study in hartley albino guinea pigs - modified buehler design, DACO: 4.6.6
2277921	2009, Waiver Rationale for the Requirement for Acute Toxicity Testing for Recruit HD, DACO: 4.1,4.6.1,4.6.2,4.6.3,4.6.4,4.6.5,4.6.6
2277842	2002, XDE-007: limited pharmacokinetics and metabolism of 14c-labeled xde-007 following a single oral administration in fischer 344 rats, DACO: 4.5.9
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2495529	2003, XDE-007: pharmacokinetics and metabolism in fischer 344 rats (Part A), DACO: 4.5.9
2495530	2004, XDE-007: pharmacokinetics and metabolism in fischer 344 RATS (Part B), DACO: 4.5.9
2277840	2001, evaluation of xde-007 in the in vivo mouse micronucleus assay, DACO: 4.5.7
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2495527	2001, evaluation of xde-007 in an in vitro chromosomal aberration assay utilizing rat lymphocytes, DACO: 4.5.6

2495528	1997, Screening of XR-007 in an in vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.5.6
2277838	2001, evaluation of xde-007 in the chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (cho/hgprt) forward mutation assay, DACO: 4.5.5
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2277834	2000, DER - oral gavage developmental toxicity study in new zealand white rabbits, DACO: 4.5.3
2277831	2000, XDE-007: oral gavage developmental toxicity study in cd rats (Prenatal Developmental Toxicity Study - Rat), DACO: 4.5.2
2277832	2000, DER - oral gavage developmental toxicity study in cd rats (Prenatal Developmental Toxicity Study - Rat), DACO: 4.5.2
2277828	2004, XDE-007: two-generation dietary reproduction toxicity study in cd rats, DACO: 4.5.1
2277830	2004, Summary - two-generation dietary reproduction toxicity study in cd rats, DACO: 4.5.1
2495526	2004, XDE-007 : one-generation dietary reproduction toxicity study with cross-fostering in cd rats, DACO: 4.5.1
2534491	2015, Review of Two-Generation Reproductive Toxicity Study (laboratory Report Number 021115) conducted with XDE-007 (Noviflumuron), DACO: 4.5.1
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2277814	2002, XDE-007: 90-day dietary toxicity study with 28-day recovery in beagle dogs, DACO: 4.3.2
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2277810	1999, XDE-007: A Dermal Sensitization Study In Guinea Pigs Maximization Design, DACO: 4.2.6
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3.0 Environment

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4.0 Value

PMRA Document Number	Reference
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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

Holson, J.F., Nemec, M.D., Stump, D.G., Kaufman, L.E., Linstrom, P., Varcho, B.J., 2009. Chapter 9: Significance, reliability, and interpretation of developmental and reproductive toxicity study findings. In Developmental and Reproductive Toxicology: A Practical Approach, Second Edition, Edited by R.D. Hood. Informa Healthcare USA, New York.

2.0 Value

PMRA Document Number	Reference
2291770	Daiker, D.H, 2011, Evaluation of Annual Replenishment of Noviflumuron bait in the prevention of termite infestation in new construction Florida Department of Agriculture and Consumer Services. DACO: 12.5.10
2291772	Foos, J.F. and D.H. Daiker, 2003, Evaluation of noviflumuron in a bait system for the prevention of termites in new construction. Florida Department of Agriculture and Consumer Services. DACO: 12.5.10
2291773	California Department of Pesticide Regulation Public Report, 2003-5: Noviflumuron. DACO: 12.5.10
2291774	Smith M.S. et. al., 2002. Proceedings of the 4th International Conference on Urban Pests. DACO: 10.2.3.4
2291775	Miller, D.M., 2010. Subterranean Termite Treatment Options. Virginia Cooperative Extension. DACO: 10.2.4

2291776 Clement, J.L., et. al., 1996. Elimination of Foraging Populations of *Reticulitermes santonensis* in one street of Paris, France, using hexaflumuron baits. Proceedings of the Second International Conference on Urban Pests. DACO: 10.2.4, DACO: 10.2.4

2291785 Ferrari, R. and M. Marini. 1999., Subterranean Termite *Reticulitermes* spp. (Isoptera: Rhinotermitidae) Baiting and Control in Historical Public Buildings in Italy. Proceedings of the 3rd International Conference on Urban Pests. DACO: 10.2.4, DACO: 10.2.4

2291814 Quarles, W., 2003. IPM for Termites - Termite Baits. IPM Practitioner XXV. DACO: 10.2.4, DACO: 10.2.4

2291815 Eger, J.E. Jr. et. al., 2012. Elimination of Subterranean Termite (Isoptera: Rhinotermitidae) Colonies Using a Refined Cellulose Bait Matrix Containing Noviflumuron When Monitored and Replenished Quarterly. J. Econ. Entomol. 105(2): 533-539. DACO: 10.2.3.4, DACO: 10.2.3.4

2291816 Spomer, N.A. and Kamble, S.T., 2005. Effect of temperature on noviflumuron performance against the eastern subterranean termite (Isoptera: Rhinotermitidae). Sociobiology. vol. 46, no. 2, pp. 335-348. DACO: 10.2.3.2, DACO: 10.2.3.2

2291817 Spomer, N.A. and Kamble, S.T., 2006.Temperature Effect on Kinetics of Uptake, Transfer, and Clearance of [14C]Noviflumuron in Eastern Subterranean Termites (Isoptera: Rhinotermitidae). Journal of Economic Entomology. Vol. 99, no. 1, DACO: 10.2.3.2, DACO: 10.2.3.2

ii) Unpublished Information

1.0 Environment

2299542 US Data Evaluation Report on the hydrolysis of benzylurea, DACO: 12.5.8

2299545 US Data Evaluation Report on the aerobic biotransformation of benzyl urea in soil, DACO: 12.5.8

2299546 US Data Evaluation Report on the adsorption-desorption of benzyl urea in soil, DACO: 12.5.8